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A remarkable accelerating effect of iodide ions in the photostimulated phosphorylation of bromoaromatic compounds

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Abstract

We find that 1 equiv. of NaI greatly accelerates the photostimulated substitution ($S_{RN}1$ mechanism) of bromobenzene, bromotoluenes and bromopyridines by diethylphosphite ion, in acetonitrile/tetrahydrofuran mixtures. Consequently, bromoaromatic compounds are suitable for preparative use.

Introduction

Phosphonylation at the sp^2 -hybridized carbon atoms of aromatic compounds under the photostimulated $S_{RN}1$ reaction conditions is now well established and fully documented [1]. Sodium or potassium salts of dialkylphosphites, generated from solutions of alkaline metals in liquid ammonia proved to be excellent nucleophiles towards variously substituted aryl iodides [2–4].

To overcome the problem of limited solubility in liquid ammonia, dimethylsulfoxide has been used occasionally as solvent [5]. We recently obtained excellent results in an acetonitrile/tetrahydrofuran mixture for the phosphorylation of iodoanilines and iodopyridines at room temperature [6].

The greatest limitation to the widespread applicability of the $S_{RN}1$ procedure lies in the preference for iodine-containing substrates, which are often expensive, not readily accessible, and unstable. Although some substitution has been observed with bromoaryls, Bunnett and Traber reported that bromobenzene reacted 1000

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Table 1

Influence of NaI on the photophosphonylation of bromotoluenes

Run	Substrate	NaI (equiv.)	Product (%) ^a
1	1- <i>o</i>	0	2- <i>o</i> (40)
2	1- <i>o</i>	0.05	2- <i>o</i> (60)
3	1- <i>o</i>	1	2- <i>o</i> (95)
4	1- <i>m</i>	0	2- <i>m</i> (49)
5	1- <i>m</i>	1	2- <i>m</i> (99)
6	1- <i>p</i>	0	2- <i>p</i> (47)
7	1- <i>p</i>	1	2- <i>p</i> (84)

^a Extent of the reaction (determined by GPC) after 10 h of illumination.

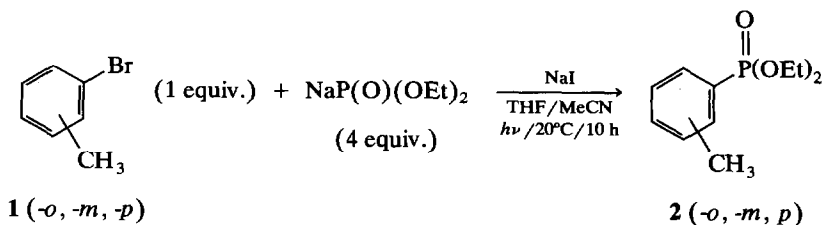
times more slowly than iodobenzene with the diethylphosphite ion [7]. Chloro- and fluoro-benzenes are not generally used in such syntheses.

During recent work [8] devoted to the synthesis of phosphonophenylalanines [9], we noted a significant acceleration in the photostimulated phosphonylation of *ortho*-bromotoluene upon addition of sodium iodide to the reaction mixture. We decided to extend the procedure to other bromoaromatic compounds.

Results and discussion

When *o*-bromotoluene was subjected to photophosphonylation with a fourfold excess of sodium diethylphosphite (generated from diethylphosphite and NaH in a THF/MeCN (1:4 v/v) mixture [6]), for 10 h at room temperature, in a Hanovia photochemical reactor (medium pressure arc tube), the extent of substitution, evaluated by GPC, was about 40%. By addition of a catalytic amount (0.05 equiv.) of dried NaI, the extent of the reaction reached 60% and was finally quasi-quantitative upon addition of 1 equiv. of NaI (runs 1–3, Table 1). An analogous accelerating effect due to NaI was observed with *m*- and *p*-bromotoluenes (runs 4–7, Table 1) (Scheme 1).

In another set of experiments, we compared the extent of photophosphonylation of bromo- and chloro-benzenes with (1 equiv.) and without NaI. The results are reported in Fig. 1. The photophosphonylation curve of iodobenzene (a) obtained under the same conditions (without NaI) served as reference. Curves (b) and (c) provided striking evidence of the impressive promoting effect of iodide ions. On the other hand, with chlorobenzene, addition of NaI had only a minor effect on an already low yield of substitution [curves (d) and (e)].



Scheme 1.

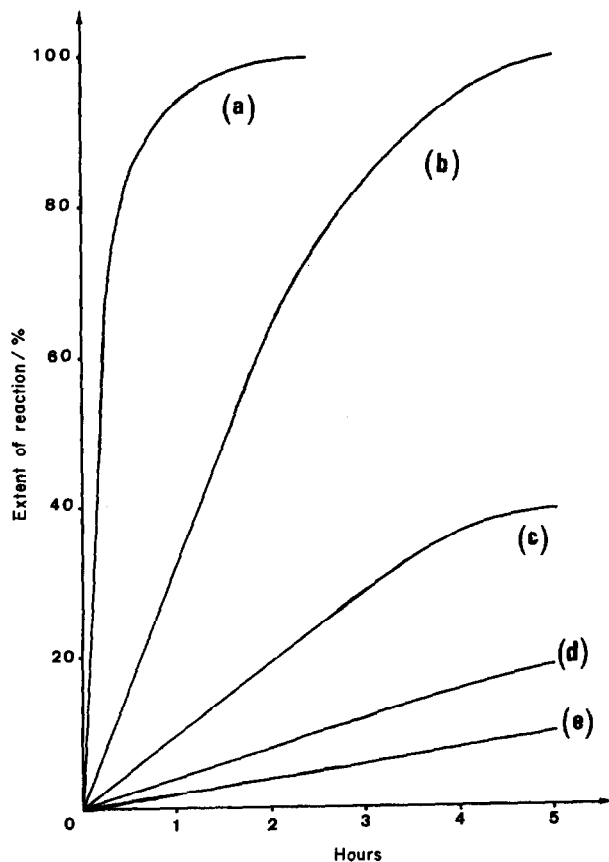


Fig. 1. Influence of NaI on the photophosphonylation of halobenzenes. (a) iodobenzene; (b) bromobenzene + NaI; (c) bromobenzene; (d) chlorobenzene + NaI; (e) chlorobenzene.

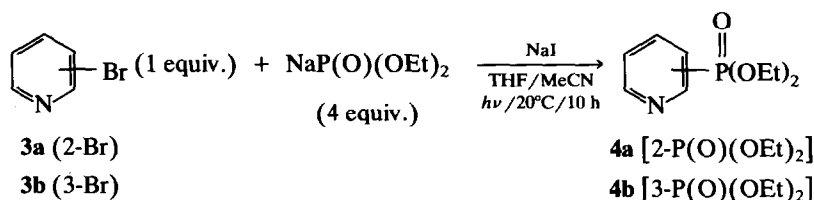
Finally, we examined bromopyridines. Bromo- and 2-chloro-pyridines react smoothly with α -stabilized carbanions under $S_{RN}1$ conditions [10–12]. We previously described the photophosphonylation of 2- and 3-iodo- and bromo-pyridines and found that whereas iodopyridines were quantitatively phosphonylated under the conditions described (THF/MeCN, 20°C, $h\nu$, 2.5 h), bromopyridines were less

Table 2

Influence of NaI on the photophosphonylation of bromopyridines

Run	Substrate	NaI (equiv.)	Reaction time (h) ^a	Product ^b
8	3a	0	5	4a
9	3a	1	3	4a
10	3b	0	11	4b
11	3b	1	5	4b

^a Time required to observe the complete disappearance of the substrate (determined from GPC measurements). ^b Phosphonopyridines were isolated and characterized (Experimental section).



Scheme 2.

reactive (78 and 40% yields for the 2-bromo- and 3-bromo-isomers, respectively) [6]. We report here (Table 2) a comparative study of the influence of NaI in the photophosphonylation of these bromopyridines (Scheme 2).

The accelerating effect of NaI was especially significant for 3-bromopyridine (runs 10 and 11, Table 2), because they show that it may be used synthetically in place of 3-iodopyridine. The case of the 2-bromopyridine was not so spectacular, because it photophosphonylates relatively easily without NaI (runs 8 and 9, Table 2).

We confirmed by GPC the absence of any iodinated intermediate substrate during these experiments. However, in view of the great difference of reactivity of brominated and iodinated aromatic compounds towards photophosphonylation, even a slight bromide-iodide exchange (certainly at equilibrium) could explain the observed kinetic effect [13*]. As a test, we illuminated bromobenzene in the presence of 1 equiv. of NaI and after 2 h we detected about 2% (GPC) of iodobenzene in the reaction mixture. Consequently, it would seem that formation of iodobenzene by bromide-iodide exchange is the limiting step of the reaction.

Moreover, we suppose that the easy diphosphonylation (87% after 60 min) of the *m*-bromiodobenzene, reported by Bunnett and Traber [7] is due to the progressive release of iodine ions during the reaction, and which catalyzed the substitution. Further, the slow diphosphonylation (52% after 20 min and 69% after 120 min) of *m*-dibromobenzene [14] seems to support that hypothesis.

An alternative hypothesis concerning the observations could concern the participation of iodide ions in the activation step, for example by forming a photoinduced charge-transfer complex with the nucleophile [15*].

Experimental section

Photostimulated reactions were conducted at room temperature in a 1 l Hanovia photochemical reactor equipped with a medium pressure mercury arc tube and protected from the atmosphere by a slight flow of argon. Substrates and solvents were dried and distilled before use. NaI was dried at 300°C for 10 h and stored at 100°C. Gas chromatography (GPC) was performed on a Delsi IGC 121 FL chromatograph equipped with a 2-m OV 17 column and an IRC-1B Intersmat integrator. The internal reference was hexadecane for bromobenzene and 1-phenyloctane for bromotoluenes and bromopyridines. Structures of products isolated

* Reference number with asterisk indicates a note in the list of references.

Table 3

³¹P-NMR, yields and boiling points of phosphonates 2 and 4

Phosphonate	³¹ P-NMR (CDCl ₃) δ (ppm)	Yield (%) ^a	B.p. (°C/mmHg) (Lit.)
2- <i>o</i>	18.1	85	96/0.2 (94–95/0.2 [7])
2- <i>m</i>	18.0	87	112/0.7 (92–93/0.02 [7])
2- <i>p</i>	18.1	77	100/0.3 (148–149/4 [16])
4- <i>a</i>	10.0	81	110/0.3 (96–97/0.03 [17])
4- <i>b</i>	15.2	80	110/0.2 (95–98/0.04 [18])

^a Yields of distilled products pure by GPC, and ³¹P and ¹H NMR.

were checked by ¹H and ³¹P NMR spectroscopies using a Bruker AC 200 spectrometer.

General procedure

NaH (0.04 mol, previously washed in hexane) and THF (25 ml) were placed in the photochemical reactor. A solution of diethylphosphite (0.04 mol) in THF (5 ml) was dropped into the magnetically stirred suspension of NaH and stirring continued until dihydrogen evolution ceased. Then, GPC internal reference, the brominated compound (0.01 mol), acetonitrile (120 ml), and NaI (0.01 mol) were introduced successively. Reaction progress was monitored by GPC. All the reactions were clean; we detected only the phosphonates 2 or 4 as products. We isolated these phosphonates after hydrolysis of the mixture and the usual workup. The phosphonates exhibited physical and spectroscopic properties in accordance with their structures and with previously published data (Table 3).

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